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(c) nucleic acids encoding an antisense RNA which inhibits expression of p53.

REMARKS

Claims 16-26 are under consideration. Claims 27-31 have been withdrawn from consideration as allegedly being drawn to a nonelected invention. Applicants acknowledge the withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, in view of the Petition Decision dated October 20, 2002.

Claims 16, 17, 19-22, 25, and 26 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Michalovitz *et al.* (*Cell*, 62:671-690, 1991, Michalovitz 1") in view of Moberg *et al.* (*J. Cell. Biochem.*, 49:208-215, 1992) and Le Gal La Salle *et al.* (*Science*, 259:988-990, 1993). Office Action, page 2. According to the Examiner, Michalovitz 1 reports that "a p53 mutant suppresses transformation of wild type p53." *Id.*, page 3. Also according to the Examiner, Moberg reports the co-transfection of a c-myc promoter construct with expression vectors expressing wild-type or mutant p53. *Id.* Finally, the Examiner asserts that Le Gal La Salle reports the use of adenoviral vectors to transfer genes into brain. *Id.* According to the Examiner, the motivation to make a recombinant virus comprising a mutant p53 gene is provided by Michalovitz 1, which reports the use mutant p53 to inhibit the expression of wild-type p53.[1] *Id.*

[1] Applicants take exception to the Examiner's allegation that they have only cited part of the case law concerning motivation to combine references. Office Action, page 3. In the Amendment filed August 9, 2002, Applicants stated: "To establish a *prima facie* case of obviousness, there must be some teaching, suggestion, or motivation in the prior art to lead one of ordinary skill in the art to modify or combine the teachings of the references in the manner proposed by the Office." As the Examiner correctly notes, the prior art includes, not just the references cited by the Office, but also the knowledge of one skilled in the art and the nature of the problem to be solved. *See, e.g.*, M.P.E.P. § 2143.01.

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Applicants traverse. As an initial matter, Applicants note that the Examiner has mischaracterized the teachings of both Michalovitz 1 and Moberg. The Examiner states "the knowledge that a p53 mutant suppresses transformation of wild type p53 is present in Michalovitz 1." *Id.* In fact, Michalovitz 1 reports that "[m]utant p53 can contribute to transformation, while wild-type (wt) p53 is not oncogenic and actually inhibits transformation." Michalovitz 1, abstract. This is exactly the opposite of the Examiner's statement. Similarly, although Moberg does report the co-transfection of a c-myc promoter construct with expression vectors expressing wild-type or mutant p53, as asserted by the Examiner, Moberg's results have nothing to do with the instant invention. In fact, Moberg reported that wild-type p53 inhibited transcription from the c-myc promoter. Moberg, abstract. Mutant p53, the subject of the rejected claims, had no effect. *Id.* In other words, Moberg provides no teaching to lead one skilled in the art to do *anything* with mutant p53.

Moreover, the Examiner has still failed to provide the motivation to combine Michalovitz 1 with Moberg and Le Gal La Salle required to make a *prima facie* case of obviousness. Although the Examiner asserts that the necessary motivation may come from, not only from the references themselves, but also from the "knowledge of [sic, one] skilled in the art known to be of interest in [sic, the] particular field," the Examiner cites no such general knowledge and again relies only on the alleged teachings of the references.

Those references on their face completely fail to provide the motivation to make the instant invention: a recombinant virus comprising *inter alia* mutant p53. Michalovitz 1 discloses that mutant p53 is oncogenic. Michalovitz 1, abstract. If anything,

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therefore, Michalovitz 1 might motivate one skilled in the art to use mutant p53 to make transformed cells. Although one skilled in the art could certainly insert the mutant p53 gene of Michalovitz 1 into an adenoviral vector according to Le Gal La Salle, the Examiner has pointed to no motivation in the references or elsewhere to make that oncogenic virus. Moberg adds no motivation to use p53 for any purpose. Moberg merely discloses that mutant p53 has no effect on transcription from the c-myc promoter. Moberg, abstract. "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." M.P.E.P. § 2143.01 (emphasis original) *quoting In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). Here, nothing in the prior art suggests the desirability of making an oncogenic adenovirus using mutant p53.

Claims 16-20, 22, 23, 25, and 26 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Levrero *et al.* (*Gene*, 101:195-202, 1991) taken with Michalovitz *et al.* (*J. Cell. Biochem.*, 45:22-29, 1991, "Michalovitz 2") and Funk *et al.* (*Mol. Cell. Biol.*, 12:2866-2871, 1992), and further in view of Chopp *et al.* (*Biochem. Biophys. Res. Comm.*, 182:1201-1207, 1992). Office Action, page 4. According to the Examiner, Levrero discloses a defective recombinant adenovirus into which the hepatitis B virus *s* gene or the chloramphenicol acetyltransferase gene has been inserted. *Id.* The Examiner further asserts that Michalovitz 2 discloses mutated mouse p53 cDNAs and the ability of mutated p53 to interfere with the function of wild-type p53. *Id.* According to the Office, Funk discloses DNA binding site for p53 with sequence SEQ ID NO:2. *Id.* The Examiner contends that "[t]he application of these nucleic acids

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to p53 expression is relevant due to the association of p53 with severe ischemic cell damage disclosed by Chopp et al." *Id.*

Applicants again traverse. The combination of Levrero with Michalovitz 2 and Funk is no different from the combination of Michalovitz 1 with Moberg and Le Gal La Salle. One skilled in the art would expect either combination of references to produce oncogenic viruses. Neither the references themselves not anything else in the prior art provide the necessary motivation to make such viruses.

In an effort to provide the missing motivation, the Examiner adds Chopp to the mix. But Chopp is woefully inadequate and, at best, renders the instant invention obvious to try. As the Federal Circuit explained in *In re O'Farrell*:

> The admonition that "obvious to try" is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

853 F.2d 894, 903, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988) (citations omitted).

Chopp reports that p53 immunostaining is increased in necrotic areas of the rat brain after an ischemic incident. Chopp, abstract. This observation, however, is clearly preliminary and provides neither the motivation nor the reasonable expectation of success necessary to support a *prima facie* case of obviousness. In fact, Chopp states:

> We have not yet determined, via DNA fragmentation studies, whether apoptosis is the mechanism of neuronal

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> death. *Our data also cannot distinguish whether p53 is simply secondary to cell death, or causes cell death.*

Chopp, 1203 (emphasis added). According to Chopp, their data merely lend "credence to a role for p53 in ischemic cell damage." *Id.*

In making the instant rejection, the Examiner attempts to bootstrap Chopp's suggestion that p53 may play a role in ischemic cell death into a motivation to express oncogenic p53 mutants or binding sites in viral vectors. In fact, there is no evidence of record to suggest that p53 mutants or binding sites with effects on oncogenesis[2] would have *any* activity in either enhancing or antagonizing any potential effect of wild-type p53 on cell death. This is precisely the type of "obvious to try" rejection the Federal Circuit warned against when the prior art provided nothing more than an invitation "to explore a new technology or general approach that seemed to be a promising field of experimentation" but "gave only general guidance as to the particular form of the claimed invention or how to achieve it." *O'Farrell*, 853 F.2d at 903, 7 U.S.P.Q.2d at 1681. The Examiner cannot now properly reject claims 16-20, 22, 23, 25, and 26 simply because what might have been "obvious to try" at the time Applicants made their invention, turned out to work. *See Life Technologies, Inc. v. Clontech Laboratories, Inc.*, 224 F.3d 1320, 1326, 56 U.S.P.Q.2d 1186, 1191 (Fed. Cir. 2000) ("That the inventors were ultimately successful is irrelevant to whether one of ordinary skill in the art, at the time the invention was made, would have reasonably expected success. The court's finding to the contrary represents impermissible use of hindsight-using the inventors' success as evidence that success would have been expected.").

[2] Applicants can find no evidence to support the Office's apparent conclusion that Funk suggests that p53 binding sites can be used to interfere with the function of wild-type p53.

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Finally, claims 22-26 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,087,617 to Smith taken with Soussi *et al.* (*Nucl. Acids Res.*, 16:11384, 1988), and further in view of Chopp. Office Action, page 5. According to the Examiner, Smith "discloses a method of inhibiting p53 expression in vitro and in vivo by administering nucleic acids encoding nucleic acids capable of blocking the mRNA transcribed from the p53 gene." *Id.* The Examiner acknowledges that Smith does not disclose a method using SEQ ID NO: 1, but contends that Soussi discloses a sequence identical to SEQ ID NO: 1. *Id.* Chopp is again relied on as providing the requisite motivation for combining Smith and Soussi to make the instant invention. *Id.*

Applicants traverse. Again, the Examiner has mischaracterized two of the references: Smith and Soussi. Smith does not disclose methods in which "nucleic acids encoding nucleic acids capable of blocking the mRNA transcribed from the p53 gene" are used. Instead, Smith teaches methods using antisense oligonucleotides. Smith, abstract and claims. Moreover, Soussi does not disclose an oligonucleotide with the sequence SEQ ID NO: 1 as recited by the claim 24. Rather, Soussi reports the sequence of a cDNA clone containing the complete coding region of rat p53. Nothing in Soussi or in Smith suggests an oligonucleotide with the particular sequence SEQ ID NO: 1. Additionally, neither Smith, Soussi, or Chopp teach the limitations of claims 25 (the nucleic acid is in a vector) or 26 (the vector is a replication defective virus).

This rejection also fails because, again, the Examiner has not provided the motivation to combine Smith with Soussi required to support a *prima facie* case of obviousness. As above, the Examiner attempts to use Chopp's suggestion that p53

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may play a role in ischemic cell death into a motivation to use Smith's p53 oligonucleotides to prevent toxicity in cultured neuronal cells. Again as above, there is no evidence of record to suggest that p53 oligonucleotides with effects on oncogenesis would have *any* activity in either enhancing or antagonizing any potential effect of wild-type p53 on neuronal toxicity. Without that evidence, one skilled in the art would not have been motivated to make the instant invention and would not have had a reasonable expectation of success.

In view of the foregoing amendments and remarks, Applicant respectfully requests the reconsideration and withdrawal of the rejections of claims 16-26 under 35 U.S.C. § 103(a) and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: February 19, 2003

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APPENDIX TO AMENDMENT OF FEBRUARY 19, 2003

Version with Markings to Show Changes Made

Amendments to the Claims

16. A recombinant virus selected from the group consisting of adenovirus, adeno-associated virus and herpes virus, said recombinant virus comprising a nucleic acid [encoding a mutated form of p53 which antagonizes wild-type p53-mediated neuronal cell degeneration *in vitro*] selected from the group consisting of:

(a) nucleic acids encoding a mutated form of p53 which antagonizes wild-type p53-mediated neuronal cell degeneration *in vitro*;

(b) the site for binding of p53 to DNA; and

(c) nucleic acids encoding an antisense RNA which inhibits expression of p53.

19. A recombinant virus according to claim 16, wherein said virus [further comprises a second nucleic acid encoding a mutated form of p53 which antagonizes wild-type p53-mediated neuronal cell degeneration] comprises two nucleic acids selected from the group consisting of:

(a) nucleic acids encoding a mutated form of p53 which antagonizes wild-type p53-mediated neuronal cell degeneration;

(b) the site for binding of p53 to DNA; and

(c) nucleic acids encoding an antisense RNA which inhibits expression of p53.

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22. A method of inhibiting toxicity in cultured neuronal cells comprising administering to said cells a nucleic acid [encoding a mutated form of p53 which antagonizes wild-type p53-mediated neuronal cell degeneration *in vitro*] selected from the group consisting of:

(a) nucleic acids encoding a mutated form of p53 which antagonizes wild-type p53-mediated neuronal cell degeneration *in vitro*;

(b) the site for binding of p53 to DNA; and

(c) nucleic acids encoding an antisense RNA which inhibits expression of p53.

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